

The Relationship Between Insomnia and CFS/ME: The HPA Axis as a Mediator

Master's Thesis in Clinical Psychology

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Author Note

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Abstract

Fatigue is common in the general population, and is the hallmark of chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME). Although the occurrence of sleep difficulties is known to be common in subjects with fatigue, research on insomnia in such subjects is absent. The current study sought to examine the impact comorbid insomnia has on level of fatigue in subjects with chronic fatigue. The aim of this study is to assess the relationship between insomnia and chronic fatigue, and examine if the relationship is affected by the endocrine activity in the HPA axis. The following hypotheses were tested: 1) Do patients with chronic fatigue and comorbid insomnia experience more fatigue than patients with chronic fatigue without comorbid insomnia? 2) Do patients with chronic fatigue and with initially comorbid insomnia experience more fatigue after treatment than chronic fatigue patients without comorbid insomnia? 3) Do patients with chronic fatigue who experience improvement in insomnia after treatment also experience less fatigue by the end of treatment compared with patients who do not experience improvement in insomnia? 4) Is the potential relationship between insomnia and chronic fatigue influenced by the activity of the HPA axis as expressed by variation in cortisol output measured by Trier Social Stress Test for Groups (TSST-G)? The study sample consisted of 75 patients with chronic fatigue. Thirty-three met criteria for insomnia, while 42 did not. While staying at Hysnes Rehabilitation Center in Trondheim, Norway, they received a work-related Acceptance and Commitment Therapy (ACT) treatment intervention lasting 3.5 weeks. In addition, they participated in a standardized stress test (Trier Social Stress Test) pre- and post-treatment. Saliva cortisol samples were collected during the test in order to measure variation in cortisol output. The current finding is the first description of how insomnia in patients with chronic fatigue is associated with higher levels of fatigue ($p < .05$). Further, this study gives preliminary support indicating that remission of insomnia in patients with chronic fatigue can significantly reduce levels of fatigue ($p < .05$), and furthermore improve the physiological stress-response ($p < .05$). These results might encourage clinicians to assess and provide specific treatment for insomnia in patients with chronic fatigue as this might improve their treatment results. An aim for further research should be to investigate the effect of specified treatment for insomnia in patients with chronic fatigue.

Keywords: insomnia, chronic fatigue, hypothalamic–pituitary–adrenal (HPA) axis, salivary cortisol, Trier Social Stress Test for Groups, Acceptance and Commitment Therapy

The Relationship Between Insomnia and Chronic Fatigue: The Hypothalamic–Pituitary–Adrenal Axis as a Mediator

Fatigue is a common complaint in the community. A large community survey conducted in the UK found that 27% of all adults reported significant fatigue in the week before interview (Ranjith, 2005). Fatigue is typically transient and explained by prevailing circumstances. However, some persons experience persistent and debilitating fatigue (Afari & Buchwald, 2003).

Chronic fatigue syndrome/myalgic encephalomyelitis (CFS/ME), as defined by the international consensus definition (Fakuda et al., 1994), is a condition primarily characterized by persistent and profound fatigue of at least six months duration. It causes substantial disruption to the individual's daily function. The fatigue has to be medically unexplained and not the result of ongoing exertion, and not substantially alleviated by rest. In addition to fatigue, the diagnostic criteria require the concurrence of four or more of the following symptoms: muscle- and joint-pain, headache, sore throat, impairment in memory or concentration, unrefreshing sleep and postexertional fatigue lasting more than 24 hours (Fakuda et al., 1994). To date, no diagnostic test exists for CFS/ME, and the diagnosis is made on the basis of symptom criteria and by excluding underlying medical or psychiatric conditions that may explain the fatigue (Devanur & Kerr, 2006). The prevalence rates for CFS/ME vary depending on the definition and the criteria used. Community and primary care studies have reported the prevalence to be between 0.2- 2.6% (Reid, Chalder, Cleare, Hotopf, & Wessely, 2000).

Many factors have been found to have an impact on fatigue. The nature as well as the causes of CFS/ME has been subject of much debate. Even though the etiology remains unclear, evidence exists for and against the importance of endocrine, psychological, immune and virological factors (Cho, Skowera, Cleare, & Wessely, 2006). Emotional stress may play a role in the pathogenesis of CFS/ME, and may trigger the disease in people that have a genetic risk (Devanur & Kerr, 2006). The influence stress exerts is complex and most likely a combined result of an effect on the immune responsiveness, the ability of the immune system to control and clear infections and an effect on the HPA axis (Devanur & Kerr, 2006). It is also likely that virus infection and flu-like illness may trigger the condition, and many cases of CFS/ME begin with an infection (Devanur & Kerr, 2006). Another predisposing vulnerability proposed is gender, and most studies report higher rates of CFS/ME in women (Ranjith, 2005).

One factor involved in chronic fatigue and CFS/ME that may have been overlooked is insomnia. Insomnia is present in most psychiatric conditions (Riemann, 2007) and chronic pain (de la Vega & Miró, 2013). Insomnia and psychopathology is highly comorbid, and as many as 50% to 80% that have a psychological disorder also report having sleep disturbances (Morin & Ware, 1996). The comorbidity is particularly high between insomnia, depression and anxiety (Morin & Ware, 1996). Insomnia is often seen as a secondary problem and a symptom of the primary psychological disorder commonly believed to be alleviated once the primary disease is treated. As a consequence, insomnia may be overlooked in mental health care settings and many clients are deprived from treatment (Harvey, 2001). The diagnosis of insomnia was virtually non-existent in a sample of 93% of all patients receiving treatment in mental health care in Norway (N= 40261). This was despite the fact that sleep disturbances was commonly acknowledged by both patients and clinicians (Kallestad et al., 2011). Studies have shown that treatment of insomnia not only can improve sleep, but also may have a positive effect by reducing the symptoms of the assumed “primary” disease. Cognitive Behavior Treatment for Insomnia (CBT-I) has shown an effect by reducing comorbid anxiety and mood disorder (Vallieres, Bastien, Ouellet, & Morin, as cited in Harvey, 2001). Comorbid insomnia has also been found to impact the treatment-response for depression, and studies have found that patients with depression and comorbid insomnia respond more poorly to treatment of both anti-depressants (Pigeon et al., 2008) and psychotherapy (Thase et al., 1997). Further comorbid insomnia may also lead to higher symptom severity, lower quality of life, lower levels of function and less benefit from treatment for patients in mental health care, independently of their primary diagnosis (Kallestad et al., 2012).

Concerning sleep difficulties and chronic fatigue the existing research has found that patients with CFS/ME, compared to healthy control subjects, often have longer sleep onset latencies suggesting that some patients may have difficulties initiating sleep (Jackson & Bruck, 2012). Further, studies have revealed that patients with CFS/ME have an abnormal sleep pattern and that the percentage of each sleep stage in this group differs from the control sample. Patients within this group spend more time awake and in the lighter stages of sleep (stage 1 and 2), and less time in the deeper stages of sleep (SWS and 2 sleep) (Gotts et al., 2013). Complaints of non-restorative sleep is also a hallmark and found to be present in 87-97% of CFS/ME cases identified in community studies. Even after a night with sufficient sleep duration, patients with CFS/ME typically report awakening unrestored or unrefreshed (Mariman et al., 2013). In addition to abnormal sleep pattern and non-restorative sleep, large

population-based studies have found that approximately 20% of CFS/ME patients either have obstructive sleep apnea or narcolepsy (Jackson & Bruck, 2012).

However, when it comes to insomnia, research is absent. To my knowledge no studies to date have examined the relationship between insomnia and CFS/ME. A search on PubMed for articles, in English, using the terms “*Insomnia and CFS/ME*” and “*Insomnia and chronic fatigue*” in the title or abstract retrieves no results of relevance.

There are many important questions left to answer concerning the relationship between insomnia and chronic fatigue. For example, how insomnia in patients with chronic fatigue has an effect on the fatigue, both as a predisposing, precipitating and perpetuating factor. If insomnia has a negative impact on clinical state and benefit from treatment, it would be important knowledge for clinicians. If that is the case, then insomnia should receive more attention of focus and should be taken into consideration in treatment of the chronic fatigue. It would also be of interest to see if improvement in insomnia severity after treatment may have an effect on the experienced fatigue. Further, it would be interesting to see what biological mechanisms that may underlie the potential relationship between insomnia and chronic fatigue.

An important factor involved in both insomnia and chronic fatigue is the hypothalamic–pituitary–adrenal (HPA) axis. During physical and psychological stress, the HPA axis functions to maintain homeostasis (Devanur & Kerr, 2006). The HPA axis thus plays a central role in the human stress response. The HPA axis is comprised of three components: the hypothalamus, pituitary gland and adrenal cortex (Wessely, Hotopf, & Sharpe, 1998). Under stress, the neurosecretory cells of the paraventricular nucleus (PVN) of the hypothalamus secrete corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) into the microportal circulatory system of the pituitary stalk. Further, CRH and AVP stimulate the release of adrenocorticotrophic hormone (ACTH) from the anterior lobe of the pituitary, and ACTH in turn promotes the release of the glucocorticoid cortisol from the adrenal cortex. The final product of the HPA axis, cortisol, is a key hormone secreted during the stress response and has a range of central and peripheral effects. These include the coordinating of circadian events such as the sleep/wake cycle and facilitating our ability to adapt to, and recover from, stress as well as promotion of learning and memory processes (Watson & Mackin, 2008) (see Figure 1). Cortisol is also essential for normal immunity and inhibits various immune activities (Dunn, 2007).

(Insert Figure 1 here)

Numerous studies have examined the HPA axis in CFS/ME, and evidence suggests a dysregulation in the function of the HPA axis (Cleare 2003; Giorgio, Hudson, Jerjes & Cleare 2005; Jackson & Bruck 2012). The dysregulation is manifested as either hypo- or hyper-activity, but a lack of variability in the hormonal expression could be the common factor (Björntorp & Rosmond 2000; Kudielka, Bellingrath, & Hellhammer 2006; Petrowski, Herold, Joraschky, Wittchen & Kirschbaum 2010). This low variability has been claimed to be a physiological expression of vital exhaustion, a mental state where the ability to adapt to stress is disrupted (Appels, 2004).

The idea that sustained arousal may disrupt the stress response, is in line with the cognitive activation theory of stress (CATS) by Ursin and Eriksen (2004). According to this theory an HPA axis dysregulation may be the result of a sustained activation over time, and may eventually lead to pathology. A study by Lutgendorf et al. (1995) examined the effects of stress on physical symptoms and functional impairments in a sample of patients with CFS/ME. Their findings showed that stress exacerbate the symptoms of fatigue.

An earlier study by Poteliakhoff (1981) showed that cortisol levels in patients with CFS/ME are reduced, and it is suggested that initial stress results in a prolonged hyperactivation of the HPA axis. Subsequently the prolonged hyperactivation leads to an insensitivity and HPA axis hypoactivation. A review by Cleare (2003) on research assessing the function of the HPA axis revealed that about half of the studies found evidence for lowered cortisol levels in patients with CFS/ME. Observations of conditions where low circulating cortisol are characterized by fatigue have led to the hypothesis that fatigue in CFS/ME is mediated by lack of cortisol (Cleare, 2003). In a later article, however, Cleare (2004) argues that one cannot know if the observed dysfunction in the HPA axis is the aetiology of the disease. It may also be secondary to other factors such as sleep disturbances.

In addition to its central role in the human stress-response system, the HPA axis plays an important role in sleep regulation and interacts with sleep in multiple ways (Buckley & Schatzberg 2005; Jackson & Bruck 2012). The HPA axis plays important roles in modulating sleep and a dysfunction in this axis can disrupt sleep (Buckley & Schatzberg, 2005). HPA axis dysfunction may play a causative role in some clinical sleep disorders such as insomnia. In insomnia the cortisol levels are increased, particularly in the evening and the first part of the nocturnal sleep period (Buckley & Schatzberg, 2005). HPA hyperactivity can have many negative effects on sleep. An increased HPA activity promotes sleep fragmentation and

shortened sleep time. Sleep fragmentation further increases cortisol levels, and thereby exacerbate the HPA axis dysfunction, leading to a vicious cycle of chronic insomnia (Buckley & Schatzberg, 2005).

Accordingly, both insomnia and CFS/ME is associated with a dysfunction in the HPA axis (Buckley & Schatzberg 2005; Cleare 2003). It is possible that the HPA axis mediates the relationship between fatigue and insomnia. However, while CFS/ME is associated with a hypoactivation, insomnia is associated with a hyperactivation.

The release of cortisol is considered a reliable HPA axis marker for the response to acute psychosocial stress. Cortisol can be measured in blood or saliva, and after stimulation onset, the cortisol levels gradually increase within a few minutes and reach a peak in concentration about 10-30 minutes after stress cessation (Foley & Kirschbaum, 2010). There is considerable variation between individuals when it comes to cortisol response to acute psychosocial stress (Foley & Kirschbaum, 2010).

Salivary cortisol levels are by most studies considered as a reliable measure of the HPA axis adaption to stress (Hellhammer, Wüst, & Kudielka, 2009). When it comes to salivary cortisol measures, the most frequently used psychological protocol in stress research is the Trier Social Stress Test (TSST) (von Dawans, Kirschbaum, & Heinrichs, 2011). The test is shown to induce significantly increase in cortisol, has large effect sizes and high reliability (von Dawans et al., 2011). The benefit using TSST is that it makes it possible to measure variability in cortisol output in response to stress (Kirschbaum, Pirke, & Hellhammer, 1993).

The aim of this study is to assess the relationship between insomnia and chronic fatigue, and examine if the relationship is affected by the endocrine activity in the HPA axis. More specifically: 1) Do patients with chronic fatigue and comorbid insomnia experience more fatigue than patients with chronic fatigue without comorbid insomnia? 2) Do patients with chronic fatigue and with initially comorbid insomnia experience more fatigue after treatment than chronic fatigue patients without comorbid insomnia? 3) Do patients with chronic fatigue who experience improvement in insomnia after treatment also experience less fatigue by the end of treatment compared with patients who do not experience improvement in insomnia? 4) Is the potential relationship between insomnia and chronic fatigue influenced by the activity of the HPA axis as expressed by variation in cortisol output measured by Trier Social Stress Test for Groups (TSST-G)?

Method

Participants

Participants were recruited from a clinical setting during 2012. General practitioners referred patients to a 3.5 week in-patient intervention at Hysnes Rehabilitation Center in Trondheim, Norway. The patients had to be between 18 and 59 years of age, on sick leave longer than 8 weeks due to experiences of chronic fatigue, musculoskeletal pain and/or diagnosed with minor mental disorders such as anxiety and depressive disorders. Prior to intervention the participants answered an extensive web-based survey provided by CheckWareTM. The survey included measures of socio-demographics, fatigue, pain, mental distress and sleep problems. Exclusion criteria were severe mental or somatic disorders as well as pregnancy. Patients were also excluded from participation if they were on medications that could affect cortisol secretion. As inclusion criteria for the current study, the participants had to score 5 or above on Chalder Fatigue Scale (Chalder et al., 1993). According to Chalder et al. (1993) a score above 5 may be considered a case of chronic fatigue.

A total number of 75 patients (one missing) met criteria for chronic fatigue at pre-treatment. They were between 22 and 59 years old, with a mean age of 41.5 years ($SD=10.3$). Fifty-eight (76.3%) were females and 16 (21.1%) were males. Moreover, 42 of the patients (56%) had chronic fatigue without insomnia, while 33 patients (44%) had chronic fatigue with comorbid insomnia. The patients also participated in a standardized stress test (Trier Social Stress Test) pre- and post-intervention. All patients except two participated in the standardized stress test pre-treatment, of those 42 also participated in the standardized stress test post-treatment.

The study was approved by the Regional Ethical Committee for Research in Health in Trondheim, Norway. Before inclusion the participants received information about the experiment, and informed consent was obtained from all subjects included in this study.

Treatment

Acceptance and Commitment Therapy (ACT) was the treatment intervention in this study. ACT is a third-wave cognitive behavior intervention approach developed by Steven Hayes (Hayes, Strosahl, & Wilson, 1999). Relational frame theory (RFT), a theory of human language and cognition, is the theoretical foundation underlying ACT (Hayes, Luoma, Bond, Masuda, & Lillis, 2006). The intervention is designed to increase psychological flexibility; “the ability to contact the present moment more fully as a conscious human being, and to change or persist in behavior when doing so serves valued ends” (Hayes et al., 2006, p.7). Psychological flexibility is established by focusing on strengthening six core processes:

acceptance, contact with the present moment, values, committed action, self as context and defusion (see Figure 2). These processes help to establish change and persistence linked to chosen values, and the approach relies on metaphors, paradoxes, stories, and exercises when working with these therapeutic components (Hayes et al., 1999). ACT encourages the patient to increase acceptance of subjective experiences in order to promote focus on chosen valued oriented goals and behavior change that can result in improved life quality (Hayes et al., 1999).

(Insert Figure 2 here)

In the present study a specific ACT manual was developed, focusing on getting people back to work after sick leave. The participants, when staying at the Hysnes Rehabilitation Center, received work-focused ACT over a period of 3.5 weeks consisting of eight group sessions (lasting 90 minutes) and five individual consultations (lasting 45 minutes). The therapeutic tools in this ACT intervention include: 1) a *work/values compass* in order to assist the patients in identifying and raising awareness of life areas, 2) a *cognitive model* illustrating the interaction between cognitions, behavior, emotions, symptoms and the social environment, 3) a model of how chronic symptoms can develop and are maintained, 4) *mindfulness exercises*, 5) a model of communication illustrating stages and phases in communication, 6) metaphors used to show patients how control is not a useful strategy, 7) genogram, 8) overview over goals and actions, 9) an illustration and description of the transtheoretical model of change and, 10) a symptom diary. The group sessions included socialization to the ACT model, motivating the patients for change, and foreseeing barriers. Furthermore, the group sessions addressed: the issue of control; consequences of attempting to control the symptoms; family and important supporters; cognitive defusion (you are not your thoughts); communication and conflict; language; and staying committed to value-guided behavior. In the individual sessions the focus lied on identifying the patients' goals and values, and help the patients commit to his/her chosen values.

Measures

Chronic fatigue was measured pre- and post-treatment using *The Chalder Fatigue Scale* (Chalder et al., 1993). The Chalder Fatigue Scale is an 11-item self-report questionnaire assessing both mental and physical fatigue (Chalder et al., 1993). Each item has four response

categories scored bimodally 0-0-1-1. (e.g., 0= better than usual; 0= no more than usual; 1= worse than usual; 1= much worse than usual). A cut-off score indicating fatigue is ≥ 5 , lasting for six months or more (Chalder et al., 1993). The test has been shown to be highly reliable and valid (Chalder et al., 1993).

Insomnia was measured pre- and post-treatment by using *The Insomnia Severity Index (ISI)* (Bastien, Vallières, & Morin, 2001). The ISI is a seven-item self-report questionnaire measuring the nature, severity and impact of sleep problems for the past two weeks (Bastien et al. 2001; Morin, Belleville, Bélanger & Ivers 2011). The items are: 1) difficulty falling asleep, 2) difficulty maintaining asleep, 3) early morning awakenings, 4) sleep satisfaction/dissatisfaction with sleep pattern, 5) interference of sleep problems with daily functioning, 6) sleep problems being noticeable to others and 7) levels of distress/worry caused by the sleep problems. Each item is rated by using a 5-point Likert scale (e.g., 0 = no problem; 4 = very severe problem) giving a total score ranging from 0 to 28. A score between 0 and 7 indicates no clinically significant insomnia, scores between 8 and 14 indicates subclinical insomnia. The cut-off score for insomnia is recommended to be a score of 15 or above (Morin et al., 2011). Consequently, patients scoring 15 or above were classified as patients with comorbid insomnia, while patients scoring 14 or below were considered patients without comorbid insomnia. The ISI has been shown to have good reliability and validity (Bastien et al. 2001; Morin et al. 2011).

Trier Social Stress Test for Groups (TSST-G) as described in von Dawans et al. (2011) was used to create a psychosocial stressor among the participants. The TSST-G is an experimental test designed to trigger mental stress among participants under controlled conditions. TSST-G is a performance task consisting of high levels of socio-evaluative threat and uncontrollability in a group format. The test consists of a public speaking task (mock job interview) and mental arithmetic task (serial subtraction) in front of a panel of two evaluators. Each session lasted approximately 2.5 hours including a 50 minutes preparation phase, 30 minutes exposure phase and a 60 minutes recovery phase. Both sessions took place between 16:30h and 19:30h in order to control for diurnal variation in cortisol secretion.

In the *preparation phase*, the participants were instructed to prepare an application for a job of their choice and in front of an expert panel to have a 2 minutes speech concerning their suitability for employment. The participants were also told that a video camera would record the interview in order to analyze their performance. One minute before the preparation period was over the first saliva sample was collected. In the *exposure phase* each participants were given a number and by using the numbers each presentation was randomly chosen by the

test panel. A mobile dividing wall separated the participants under the experiment thereby restricting eye contact and social interaction between the participants. During the task the evaluators withheld all verbal and non-verbal feedback. The second saliva sample was collected after the presentations, and instructions were given to a mental arithmetic task. In this task the participants were asked to subtract the number 16 as quickly and correctly as possible from a number given by the test panel (3330, 3314, 3298). Each participant spent 1 minute and 20 seconds on this task, and neither here did they receive any feedback. After the arithmetic task, the third saliva sample was collected. During the recovery phase, an opportunity to share thoughts and reflections considering the experience was given to the participants. In addition, every 15 minute a saliva sample was taken (in total four salivettes)

Physiological measures were obtained during each test (pre- and post-treatment) and seven saliva samples were collected using a polyester salivette. One was taken during the preparation period, two during the experiment, and four were taken during the recovery phase. The timing of the pre-test and post-test was kept constant throughout the testing period due to diurnal variations on cortisol secretion (Chan & Debono, 2010). TSST-G has shown to induce significant increases in cortisol, and psychological stress responses (von Dawans et al., 2011).

Adrenocortical activity in response to psychosocial stress was measured using *saliva cortisol* samples as a biomarker. Cortisol as an indicator for adrenocortical activity has, by recent studies, been found to be highly predictive for psychosocial stress (Foley & Kirschbaum, 2010). Purpose-designed polyester salivettes produced by Sarstedt Inc., Rommelsdorf, Germany, were used to collect the samples and have been used in several previous studies (von Dawans et al., 2011; Witteveen et al., 2010). After sampling, the salivettes were stored at -20°C before being analyzed at the Department of Medical Biochemistry at St. Olavs Hospital, Trondheim. The samples were thawed, centrifuged and analyzed on Modular E170 from Roche using an electrochemiluminescens immunoassay (ECLIA) method. The assay used for determination of cortisol in saliva had an interassay variability of 7.9% at 12 nmol/L. To measure variability in cortisol output the last saliva sample was subtracted from the fourth sample, as recommended by von Dawans et al. (2011).

Statistical Analyses

Statistical analyses were carried out using Statistical Package for Social Sciences (SPSS) for Windows.

A hierarchical linear regression analysis was conducted to test the first hypothesis that patients with chronic fatigue and comorbid insomnia exhibit higher levels of fatigue compared to chronic fatigue patients without comorbid insomnia. Level of fatigue at pre-

treatment was used as dependent variable. In order to statistically control for potential age and sex differences age was entered in step 1 and gender was entered in step 2. In step 3, comorbid (1) or not comorbid insomnia (0) was entered as a dichotomized predictor variable.

To test the second hypothesis that patients with chronic fatigue and comorbid insomnia at pre-treatment exhibit higher levels of fatigue after treatment compared to patients with chronic fatigue without comorbid insomnia post-treatment, a second hierarchical regression analysis was conducted. Level of fatigue at post-treatment was used as the dependent variable. In order to statistically control for potential age and sex differences age was entered in step 1 and gender in step 2. In step 3 level of fatigue at pre-treatment was entered. In step 4 comorbid (1) or not comorbid insomnia (0) at pre-treatment was entered as a dichotomized predictor variable.

To test the third hypothesis (that patients with chronic fatigue who no longer meets criteria for comorbid insomnia after treatment exhibit less fatigue by the end of treatment compared to patients with no change in insomnia status before and after treatment) insomnia status at post-treatment was entered as a dichotomized new predictor variable in step 5 of the second hierarchical regression analysis. The unique explained variance from step 4 to 5 of the second hierarchical regression analysis examines to what extent a change in insomnia status predicts improvement in level of fatigue at treatment termination.

To examine to what extent insomnia status predicts variability in cortisol output two new hierarchical regression analyses were conducted. In the first regression analysis variability in cortisol output at pre-treatment was the dependent variable. Age was entered in step 1 and gender in step 2. Insomnia status at pre-treatment was the predictor variable entered in step 3. In the second hierarchical regression analysis variability in cortisol output at post-treatment was the dependent variable. Age was entered in step 1 and gender in step 2. Variability in cortisol output at pre-treatment was entered in step 3. In step 4 insomnia status at pre-treatment was entered and in step 5 insomnia status at post-treatment was entered.

Level of statistical significance was set to $p < 0.05$.

Results

To examine whether comorbid or no comorbid insomnia was predictive of level of fatigue, a hierarchical linear regression analysis was conducted in three steps. The results, summarized in Table 1, show that age entered in step 1 and gender entered in step 2 did not predict level of fatigue. However, insomnia status entered in step 3 significantly predicted

higher levels of fatigue, indicating that patients with insomnia exhibited significantly higher levels of fatigue.

(Insert Table 1 here)

To examine if patients with chronic fatigue and initial comorbid insomnia exhibit higher levels of fatigue post-treatment compared to chronic fatigue patients without comorbid insomnia pre-treatment, a hierarchical linear regression analysis was conducted. As shown in Table 2, higher age, but not gender, was significantly associated with higher levels of fatigue at treatment termination. Higher levels of fatigue at pre-treatment were significantly associated with higher levels of fatigue at post-treatment. However, insomnia status at pre-treatment did not predict levels of fatigue at treatment termination. To examine whether a change in insomnia status at treatment termination predicted levels of fatigue at post-treatment, insomnia status at post-treatment was entered as a dichotomized variable in step 5 of the hierarchical linear regression analysis. As shown in Table 2, a change in insomnia status from step 4 to step 5 significantly predicted lower levels of fatigue at post-treatment.

(Insert Table 2 here)

A hierarchical linear regression analysis was also conducted to test whether insomnia status at pre-treatment predicted variability in cortisol output on the Trier Social Stress Test at pre-treatment. Change in cortisol response was measured by subtracting the 4th from the 7th saliva sample. As shown in Table 3, there was no support for this hypothesis; patients with insomnia did not demonstrate a lowered cortisol variation in response to the TSST-G.

(Insert Table 3 here)

To examine if insomnia status pre- and post-treatment predicted variability in cortisol output at treatment termination a final hierarchical regression analysis was conducted. Variability in cortisol output at post-treatment was the dependent variable. In the first two steps age and gender were entered to control for their potential confounding effects. In the third step variability in cortisol output at pre-treatment was entered. In the fourth step insomnia status at pre-treatment was entered, while in the fifth step insomnia status at post-

treatment was entered. As shown in Table 4, neither age nor gender predicted variability in cortisol output at treatment termination, but variability in cortisol output at pre-treatment did. Insomnia status at pre-treatment did not predict variability in cortisol output at treatment termination, but a change in insomnia status from pre- to post-treatment did since insomnia status at post-treatment entered in step 5 added unique variance over and above insomnia status at pre-treatment.

(Insert Table 4 here)

Discussion

To my knowledge, this was the first study that investigated the effect of insomnia in patients with chronic fatigue. This study found that patients with chronic fatigue and comorbid insomnia experienced significantly more fatigue compared to chronic fatigue patients without insomnia. Insomnia explained 12.6% of the variance in level of fatigue between chronic fatigue patients with and without insomnia, when controlling for the effect of both age and gender. Meeting criteria for comorbid insomnia before treatment was not found to have a significant impact on level of fatigue after treatment. An interesting finding was, however, that patients who met the criteria for comorbid insomnia before but not after treatment termination, showed a significant improvement in fatigue compared to patients who met criteria for comorbid insomnia both before and after treatment. Improvement in insomnia explained 7.3% of the variance in fatigue after treatment when controlling for both age, gender and levels of fatigue at pre-treatment. Concerning the physiological mechanisms underlying insomnia and chronic fatigue, this study found a significant association between an improvement in insomnia and a more favorable physiological stress-response on the stress test after treatment. Insomnia before treatment was not associated with a more detrimental response on the TSST-G, neither pre- nor post-treatment.

This study supports the importance of stress management in patients with chronic fatigue. No medical treatment can create a normal activation in the HPA axis. Only psychological treatments focusing on cognitions, emotions and behavior can have a therapeutic impact on the HPA axis. Psychological treatment like Mindfulness-Based Stress Reduction (MBSR) has in an earlier study shown to have a significant effect on the cortisol awakening response (CAR), with cortisol levels at post-intervention showing a prolonged increase after awakening (Matousek, Pruessner, & Dobkin, 2011). Further, studies have also

revealed a significant reduction in level of stress and fatigue (Carlson & Garland, 2005). MBSR is also associated with lower afternoon cortisol levels (Witek-Janusek et al., 2008). To my knowledge, only one study to date has examined the effect MBSR has on salivary cortisol during acute stress (Nyklíček, Mommersteeg, Van Beugen, Ramakers, & Van Boxtel, 2013). This study did not find any effect, but more research is needed to verify this.

The current finding, that improvement in insomnia results in lower levels of fatigue at post-treatment, might be mediated, at least partly, by an increased normalization of the HPA axis function. A hypothesis may be that, as improvement in insomnia resulted in a more favorable cortisol response on TSST-G, which has a secondary effect on fatigue levels. If this is the case, then future research on fatigue should include measures of cortisol output. However, it is not certain that it is an initially HPA axis dysfunction which is the cause of the relationship between insomnia and chronic fatigue. It could be that anxiety and worry also have an impact on insomnia and fatigue, and that HPA axis dysfunction is a result of this.

As previously stated, insomnia is associated with an HPA axis dysfunction. As a change in insomnia status predicts a more favorable cortisol output during the stress test at post-treatment, it may be that the HPA axis dysfunction shown in many fatigue patients primarily is a result of comorbid insomnia. Thus, the current finding may support the hypothesis of Cleare (2004), claiming that the observed HPA dysfunction may occur due to factors such as sleep disturbance. However, as improvement in insomnia also were associated with a relieve in level of fatigue, it is difficult to know whether it is the relieve in insomnia or relieve in level of fatigue that is the cause of the improved cortisol output shown at post-treatment.

The participants did not receive any specific treatment for insomnia. Despite this several showed a considerable improvement in insomnia after treatment with ACT. At pre-treatment 33 patients met criteria for insomnia, while the number was reduced to 12 at post-treatment. It would have been interesting to see if a treatment intervention like Cognitive Behavioral Therapy for Insomnia (CBT-I), both alone or combined with ACT, can have an even larger effect on improving insomnia. Further, it would also be interesting to see what impact this might have on level of fatigue after treatment. Based on the findings in this study one might expect an even larger reduction in fatigue if the participants had received CBT-I instead of work-related ACT.

Research has shown that treatment of insomnia with CBT-I leads to both subjective and objective improvements in sleep quality and quantity. The effect seems to endure through 6 month follow-up (Edinger, Wohlgemuth, Radtke, Marsh, & Quillian, 2001). However, some

individuals do not respond to traditional CBT-I approaches. Additionally, for many patients, this is a very demanding and difficult treatment to go through with. Thus, a modified treatment may be useful both for enhancing the effects and improving the number of individuals that complete treatment (Dalrymple, Fiorentino, Politi, & Posner, 2010). The third generation of behavioral therapy includes ACT but also Mindfulness-Based Cognitive-Therapy (MBCT) (Hayes, 2004). These interventions target metacognitive processes rather than the content of cognitions (Ong, Ulmer, & Manber, 2012). Metacognition is typically understood as “thinking about thinking” (Flavell, 1979). Mindfulness is a central feature in both MBCT and ACT. Interventions that focus on mindfulness promote a metacognitive shift in perspective from an outcome-oriented approach to a process-oriented approach (Ong, Ulmer, & Manber, 2012). This mindful reappraisal is hypothesized to attenuate the stress reaction and the activation of the HPA axis (Ong, Ulmer, & Manber, 2012). Accordingly, the mindfulness techniques included in the ACT treatment in the present study might explain the improvement in cortisol output. Since insomnia is associated with HPA axis dysfunction, it may also explain why this improvement was associated with an improvement in insomnia.

Findings indicate that an integrated intervention combining mindfulness and CBT-I is associated with reductions in both sleep and sleep-related arousal. Ong, Shapiro, & Manber (2008) combined mindfulness meditation with behavior therapy for insomnia. They found that half of the sample experienced a 50% or greater reduction in self-reported time awake. Furthermore, at end of treatment, all but two participants no longer had clinical insomnia measured by ISI. The results also revealed a significant correlation between the total number of meditation sessions during treatment and reduction in arousal. The finding supports the hypothesis that mindfulness reduces arousal. Arousal is considered a sleep-interfering psychological process. *Sleep-interfering processes* consists of worries, negative emotions, and thoughts related to stressful events that lead to arousal and thus assumed to interfere with sleep (Lundh & Broman, 2000).

In addition to mindfulness, other components of ACT may also be helpful for treatment of insomnia. The ultimate goal of ACT, as previously stated, is to promote greater psychological flexibility (Hayes et al., 2006). This may foster a willingness to let go of the struggle to control sleep, and may thereby decrease secondary distress (e.g., frustration and anxiety) that occurs during the process, and may enhance the likelihood of falling asleep over time (Dalrymple et al., 2010). A recent study examining insomnia in chronic pain patients found a positive correlation between psychological flexibility and measures of sleep quality (McCracken, Williams, & Tang, 2011). *Cognitive defusion*, a key intervention in ACT, may

also be relevant to insomnia. In cognitive defusion dysfunctional beliefs and negative automatic thoughts are not evaluated as something negative to get rid of (Lundh, 2005). In insomnia this may lead to less focus on sleep-interpreting thoughts, another psychological process argued to be involved in insomnia (Lundh & Broman, 2000). *Sleep-interpreting processes* comprise a number of different kinds of cognitions concerning sleep; misperceptions about sleep, mistaken beliefs and attributions concerning one's sleep need and causes and consequences of poor sleep are examples of sleep-interpreting processes which may all lead to a magnification of the sleep problems (Lundh & Broman, 2000).

In patients with insomnia and chronic fatigue dysfunctional beliefs and negative automatic thoughts can be related both to sleep-difficulties, as well as to the fatigue. If that is the case, then treatment with ACT might contribute to improving both the insomnia and fatigue. Further research should investigate this more thoroughly, and examine whether the thoughts, feelings and sensations of individuals with insomnia and chronic fatigue is more related to either insomnia or fatigue.

Individuals experiencing insomnia may lose sight of some of their values in life as their focus become directed towards their sleep difficulties and trying to control their sleeplessness (Ong, Ulmer, & Manber, 2012). ACT includes tools like value compass in order to identify values linked to chosen domains, and further requires a rating of the importance of chosen values. The therapist then helps the patients see the costs of behavior in terms of a linked value. This promotes a shift in focus from symptom-reduction and focus on the sleep difficulties, to movement towards a focus on values (Dalrymple et al., 2010). For example an individual who values friendship go out to meet his or hers friends after a night with insufficient sleep, instead of staying home. Many of the components of ACT might have an effect on insomnia, and this might explain some of the improvement in insomnia found in this study.

When investigating the physiological responses to stress pre- and post-treatment, this study examined the variability in cortisol output and thus did not measure if the participants had a hypo- or hyper-activation in cortisol response. As previously stated, fatigue is associated with a hypoactivation, while insomnia is associated with a hyperactivation in the HPA axis. To my knowledge, whether chronic fatigue patients with and without insomnia differ in cortisol levels has not been examined. This would be interesting for further research to look into. A hypothesis could be that patients with chronic fatigue and comorbid insomnia possess higher levels of cortisol compared to patients with chronic fatigue without insomnia.

This study has several limitations that should be noted. First, one main limitation is its reliance on self-report outcome for CFS/ME. The participants were included in this study based on subjective symptom measures of chronic fatigue using the Chalder Fatigue Scale (symptom severity ≥ 5). A clinical diagnosis of CFS/ME was not requested or given to any of the participants. As a consequence one cannot know if the participants actually would have fulfilled the criteria for a CFS/ME diagnosis, neither if this would have had an impact on the results. A subjective measure (ISI) was also used for measuring insomnia, and the patients were diagnosed using a semi-structured interview for insomnia. This limits the conclusions that can be drawn about CFS/ME and insomnia from the current study. ISI rely on self-report and the results may have been different if objective sleep parameters such as polysomnography was included, or if a diagnosis was given by an experienced clinician. Further, as the study relied on self-report it is subject to social desirability. The participants were also referred to a treatment and this could have influenced their reporting of symptoms. Secondly, the number of missing from pre- to post-treatment should not be overlooked. From pre- to post-treatment on TSST-G, there were 31 participants missing (N= 44 post-treatment). When it comes to post-treatment measures using ISI, the number of missing from pre- to post-treatment was 27 (N= 48 post-treatment). The relatively low number of participants attending post-treatment limits the inferences that can be drawn from the current results. The results might have been different if the amount of missing data was less. Third, the study population is relatively small (N= 75), which makes generalization of this findings challenging. Fourth, the study included only two assessment points (pre and post) that do not allow for conclusions about causality. We cannot elucidate the exact relationship between insomnia and chronic fatigue, and it is impossible from the existing design to say if it is the improvement in insomnia after treatment that have an impact on fatigue, or if it is a reduction in fatigue that have effect on insomnia. Finally, lack of long- term follow-up after intervention is also a limitation. The findings in this study showed that alteration in insomnia can occur relatively quickly within the 3.5 weeks stay at Hysnes rehabilitation center. Measures at both pre- and post-treatment were taken while the patients were staying at Hysnes and we cannot know if this improvement was temporary, or if it had a long-lasting effect after the patient returned to his or her natural environment. Hence, a question left unanswered is what happened when the patients left the structured environment at Hysnes and returned to their daily livings. This is something future research should investigate.

Conclusion

Despite its limitations, the findings in the present study imply that insomnia in patients with chronic fatigue have a detrimental effect on their level of fatigue. Further, an improvement in insomnia is of importance both for treatment-response and the physiological stress-response. The findings point to the importance of clinicians identifying insomnia in patients with chronic fatigue, and further initiate treatment for this. Treatment for insomnia may reduce the levels of fatigue and improve the physiological stress-response leading to better ability to adapt to stress. The positive effect of improvement in insomnia found in this study is especially important when previously studies (Kallestad et al., 2011) have found that insomnia often is overlooked in mental health care settings. However, more research is needed to verify the findings in this study. Thus the results should be regarded as preliminary.

Based on the findings in this study an aim of future research should be to test the additive effect of providing treatment for insomnia in patients who receive treatment for chronic fatigue.

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Table 1

Summary of the Hierarchical Regression Analysis Examining the Unique Effect of Insomnia Status on Levels of Fatigue at Pre-Treatment

Step	Independent variables	B	S.E. B	β	t	p
1						
	Age	0.004	0.02	0.02	0.18	0.86
2						
	Gender	0.70	0.56	0.15	1.25	0.22
3						
	Insomnia or not at pre-treatment ^a	0.71	0.22	0.36	3.19	0.002*

Note. Dependent variable = Chalder Fatigue Scale pre-treatment.

^aInsomnia was measured using Insomnia Severity Index (ISI) ≥ 15 .

* $p < .05$.

Table 2

Summary of the Hierarchical Regression Analysis Examining the Effect of Insomnia Status at Pre- treatment and Change in Insomnia Status from Pre- to Post-Treatment has on Levels of Fatigue at Post-Treatment

Step	Independent variables	B	S.E. B	β	t	p
1						
	Age	0.19	0.06	0.46	3.48	0.001*
2						
	Gender	-0.85	1.47	-0.08	-0.58	0.57
3						
	Level of fatigue pre-treatment ^a	0.52	0.25	0.27	2.07	0.04*
4						
	Insomnia or not at pre-treatment ^b	0.24	0.58	0.06	0.42	0.68
5						
	Insomnia or not at post-treatment ^b	1.36	0.63	0.31	2.17	0.04*

Note. Dependent variable = Chalder Fatigue Scale post-treatment.

^aFatigue was measured using Chalder Fatigue Scale.

^bInsomnia was measured using Insomnia Severity Index (ISI) ≥ 15 .

* $p < .05$.

Table 3

The Summary of the Hierarchical Regression Analysis Examining the Effect Insomnia Status at Pre-Treatment has on the Change in Cortisol Response in Trier Social Stress Test (TSST-G) Pre-Treatment

Step	Independent variables	B	S.E. B	β	t	p
1						
	Age	0.08	0.05	0.18	1.51	0.14
2						
	Gender	0.16	1.29	0.02	0.12	0.90
3						
	Insomnia or not at pre-treatment ^a	0.10	0.55	0.02	0.18	0.86

Note. Dependent variable = variability in cortisol output during TSST-G at pre-treatment.

^aInsomnia was measured using Insomnia Severity Index (ISI) ≥ 15 .

* $p < .05$.

Table 4

The Summary of the Hierarchical regression Analysis Examining the Effect Insomnia Status Pre- Treatment and Change in Insomnia Status from Pre- to Post-Treatment has on the Change in Cortisol Response in the Trier Social Stress Test (TSST-G) Post-Treatment

Step	Independent variables	B	S.E. B	β	t	p
1						
	Age	-0.02	0.07	-0.05	-0.25	0.80
2						
	Gender	-0.28	1.68	-0.04	-0.17	0.87
3						
	Change in stress response pre-treatment ^a	0.29	0.14	0.40	2.06	0.05*
4						
	Insomnia or not at pre-treatment ^b	-0.53	0.60	-0.17	-0.88	0.39
5						
	Insomnia or not at post-treatment ^b	-1.67	0.70	-0.54	-2.37	0.03*

Note. Dependent variable = variability in cortisol output during TSST-G at post-treatment.

^aStress response during TSST-G was measured using saliva cortisol.

^bInsomnia was measured using Insomnia Severity Index (ISI) ≥ 15 .

* $p < .05$.

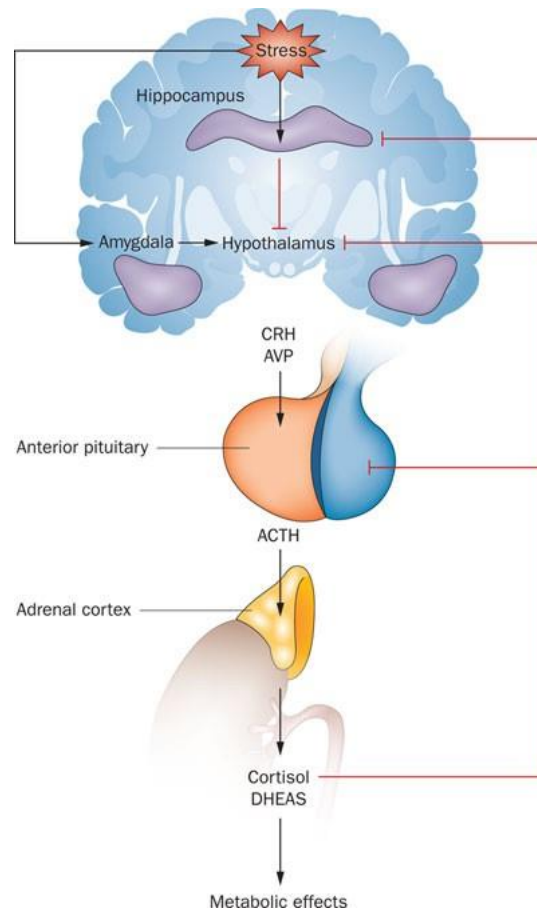


Figure 1. Schematic illustration of the hypothalamic–pituitary–adrenal (HPA) axis. Adapted from “Hypothalamic–pituitary–adrenal axis dysfunction in chronic fatigue syndrome,” by A.S. Papadopoulos, and A.J. Cleare, 2012, *Nature Reviews Endocrinology*, 8, p.26. Copyright 2012 by Macmillan Publishers.

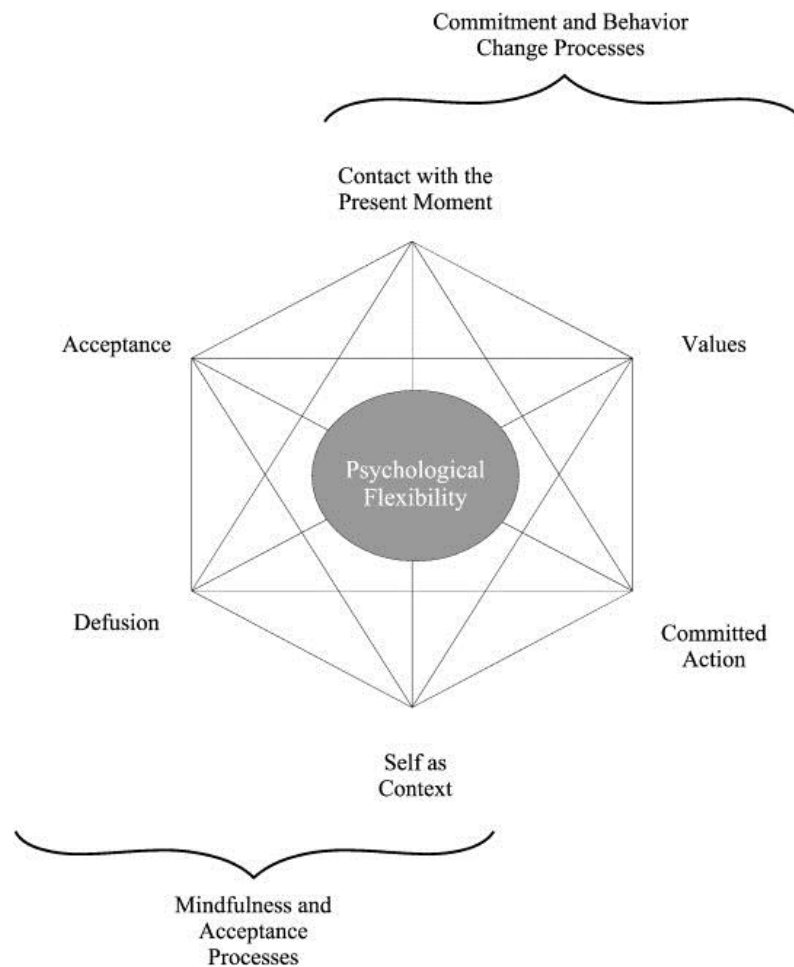


Figure 2. Illustration of the six core processes in establishing psychological flexibility in ACT. Adapted from “Acceptance and commitment therapy and contextual behavioral science: Examining the progress of a distinctive model of behavioral and cognitive therapy,” by S.C.Hayes, M.E.Levin, J.Plumb-Villardaga, J.L. Villatte, and J.Pistorello, 2013, *Behavior Therapy*, 44, p.185. Copyright 2011 by the Association for Behavioral and Cognitive Therapies.